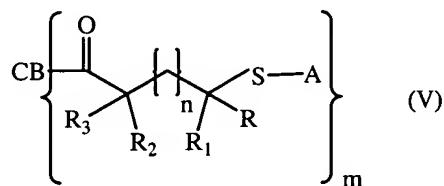


AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions and listings of claims in the application:

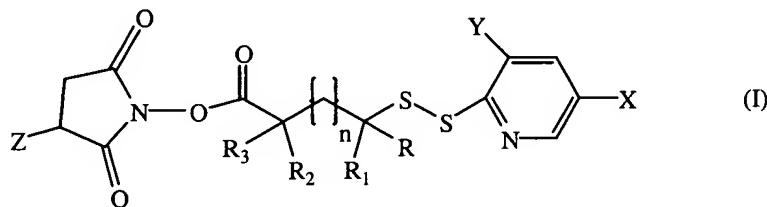
LISTING OF CLAIMS:

1. (original): A method of making a conjugate comprising a cell binding agent and one or more small molecule drugs, wherein said conjugate is represented by formula (V):



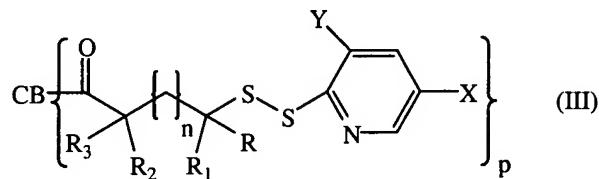
wherein CB represents the cell binding agent, A represents the small molecule drug linked by a disulfide moiety, R, R₁, R₂ and R₃ are the same or different and are H, methyl, ethyl, or linear, branched or cyclic alkyl having 3 to 6 carbon atoms, n is 0 or an integer from 1 to 4, and m is an integer of 1 to 10 or more, said method comprising:

- (1) reacting the cell binding agent with a cross-linker of the formula (I):



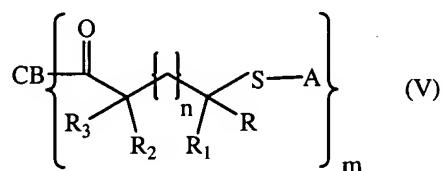
wherein X and Y are the same or different and are H, CONR₄R₅ or NO₂, provided that X and Y are not both H at the same time, R₄ and R₅ are the same or different and are each H, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, iso-butyl or tert-butyl, and Z is SO₃M⁺ or H, wherein M⁺ represents a metal ion or a tetra alkyl ammonium ion,

to thereby give a compound of the formula (III):



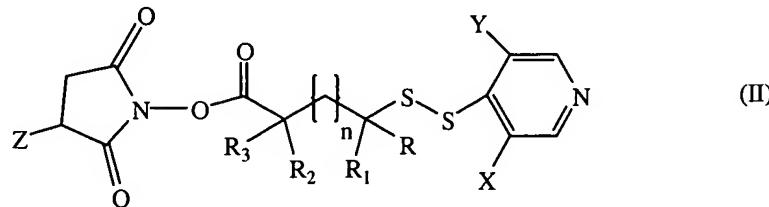
wherein p represents an integer of 1 to 10 or more, and

- (2) reacting the compound of the formula (III) with one or more small molecule drugs comprising a free thiol group.
2. (original): A method of making a conjugate comprising a cell binding agent and one or more small molecule drugs, wherein said conjugate is represented by formula (V):

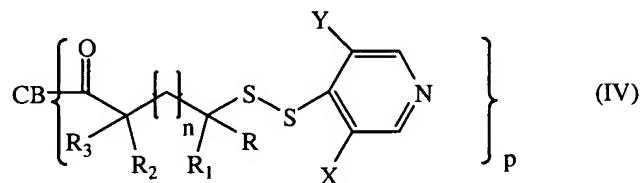


wherein CB represents the cell binding agent, A represents the small molecule drug linked by a disulfide moiety, R, R₁, R₂ and R₃ are the same or different and are H, methyl, ethyl, or linear, branched or cyclic alkyl having 3 to 6 carbon atoms, n is 0 or an integer from 1 to 4, and m is an integer of 1 to 10 or more, said method comprising:

- (1) reacting the cell binding agent with a cross-linker of the formula (II):



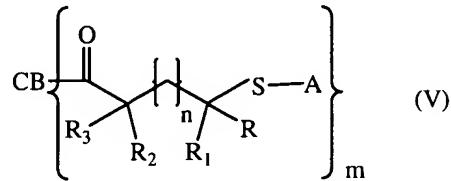
wherein X and Y are the same or different and are H, CONR₄R₅ or NO₂, provided that X and Y are not both H at the same time, R₄ and R₅ are the same or different and are each H, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, iso-butyl or tert-butyl, and Z is SO₃M⁺ or H, wherein M⁺ represents a metal ion or a tetra alkyl ammonium ion, to thereby give a compound of the formula (IV):



wherein p represents an integer of 1 to 10 or more, and

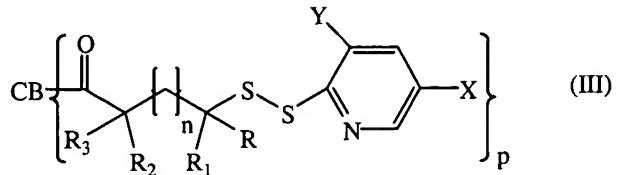
- (2) reacting the compound of the formula (IV) with one or more small molecule drugs comprising a free thiol group.
3. (original): The method of claim 1 or 2, wherein the cell-binding agent is an antibody or an antigen binding fragment thereof.
4. (original): The method of claim 1 or 2, wherein the cell-binding agent is a monoclonal antibody or an antigen binding fragment thereof.
5. (original): The method of claim 1 or 2, wherein the small molecule drug is a cytotoxic agent.

6. (original): The method of claim 1 or 2, wherein the small molecule drug is at least one member selected from the group consisting of a maytansinoid compound, a taxane compound, a CC-1065 compound, a daunorubicin compound, a doxorubicin compound, and analogues or derivatives thereof.
7. (original): The method of claim 1 or 2, wherein both of R and R₁ are H or methyl, or one of R and R₁ is H and the other is methyl.
8. (original): The method of claim 1 or 2, wherein n is 1, R₁ is methyl, and R, R₂ and R₃ are H.
9. (original): The method of claim 1 or 2, wherein n is 1 and R, R₁, R₂, and R₃ are H.
10. (original): The method of claim 1 or 2, wherein n is 1, R and R₁ are both methyl, and R₂ and R₃ are both H.
11. (original): A method of making a conjugate comprising a cell binding agent and one or more small molecule drugs, wherein said conjugate is represented by formula (V):



wherein CB represents the cell binding agent, A represents the small molecule drug linked by a disulfide moiety, R, R₁, R₂ and R₃ are the same or different and are H, methyl, ethyl, or linear, branched or cyclic alkyl having 3 to 6 carbon atoms, n is 0 or an integer from 1 to 4, and m is an integer of 1 to 10 or more, said method comprising:

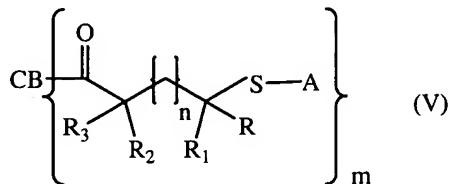
reacting a compound of the formula (III)



wherein X and Y are the same or different and are H, CONR₄R₅ or NO₂, provided that X and Y are not both H at the same time, R₄ and R₅ are the same or different and are each H, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, iso-butyl or tert-butyl, and p represents an integer of 1 to 10 or more,

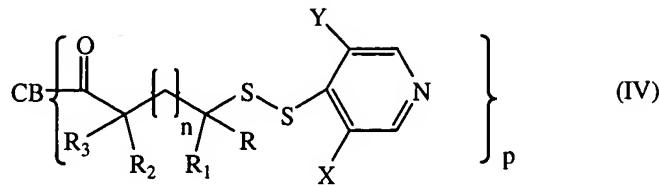
with one or more small molecule drugs comprising a free thiol group.

12. (original): A method of making a conjugate comprising a cell binding agent and one or more small molecule drugs, wherein said conjugate is represented by formula (V):



wherein CB represents the cell binding agent, A represents the small molecule drug linked by a disulfide moiety, R, R₁, R₂ and R₃ are the same or different and are H, methyl, ethyl, or linear, branched or cyclic alkyl having 3 to 6 carbon atoms, n is 0 or an integer of 1 – 4, and m is an integer of 1 to 10 or more, said method comprising:

reacting a compound of the formula (IV):



wherein X and Y are the same or different and are H, CONR₄R₅ or NO₂, provided that X and Y are not both H at the same time, R₄ and R₅ are the same or different and are each H, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, iso-butyl or tert-butyl, and p represents an integer of 1 to 10 or more,

with one or more small molecule drugs comprising a free thiol group.

13. (original): The method of claim 11 or 12, wherein the cell-binding agent is an antibody or an antigen binding fragment thereof.

14. (original): The method of claim 11 or 12, wherein the cell-binding agent is a monoclonal antibody or an antigen binding fragment thereof.

15. (original): The method of claim 11 or 12, wherein the small molecule drug is a cytotoxic agent.

16. (original): The method of claim 11 or 12, wherein the small molecule drug is at least one member selected from the group consisting of a maytansinoid compound, a taxane compound, a CC-1065 compound, a daunorubicin compound, a doxorubicin compound, and analogues or derivatives thereof.

17. (original): The method of claim 11 or 12, both of R and R₁ are H or methyl, or one of R and R₁ is H and the other is methyl.

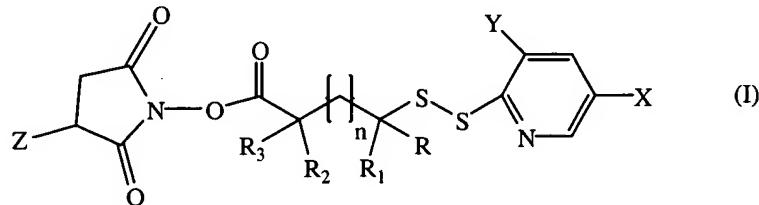
18. (original): The method of claim 11 or 12, wherein n is 1, R₁ is methyl, and R, R₂ and R₃ are H.

19. (currently amended): The method of claim 11 or 12, wherein n is 1 and R, R₁, R₂, and R₃ are H.~~20. The method of claim 11 or 12, wherein n is 1, R and R₁ are both methyl, and R₂ and R₃ are both H.~~

20-33. canceled

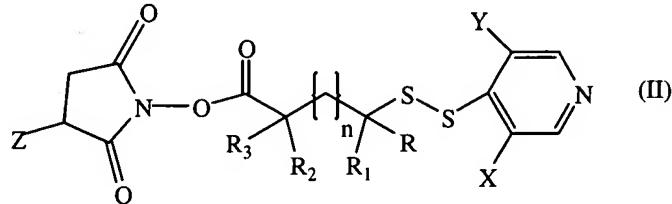
34. (new): The method of claim 11 or 12, wherein n is 1, R and R₁ are both methyl, and R₂ and R₃ are both H.

35. (new): A cross-linker of formula (I):



wherein R, R₁, R₂ and R₃ are the same or different and are H, methyl, ethyl, or linear, branched or cyclic alkyl having 3 to 6 carbon atoms, n is 0 or an integer from 1 to 4, X and Y are the same or different and are CONR₄R₅ or NO₂, R₄ and R₅ are the same or different and are each H, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, iso-butyl or tert-butyl, and Z is SO₃⁻M⁺ or H, wherein M⁺ represents a metal ion or a tetra alkyl ammonium ion, provided that when X and/or Y is NO₂, Z is not H.

36. (new): A cross-linker of formula (II):



wherein R, R₁, R₂ and R₃ are the same or different and are H, methyl, ethyl, or linear, branched or cyclic alkyl having 3 to 6 carbon atoms, n is 0 or an integer from 1 to 4, X and Y are the same or different and are CONR₄R₅ or NO₂, R₄ and R₅ are the same or different and are each H, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, iso-butyl or tert-butyl, and Z is SO₃M⁺ or H, wherein M⁺ represents a metal ion or a tetra alkyl ammonium ion, provided that when X and/or Y is NO₂, Z is not H.

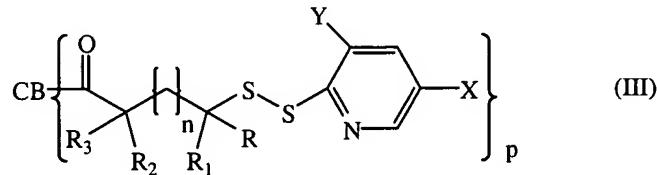
37. (new): The cross-linker of claim 35 or 36, wherein both of R and R₁ are H or methyl, or one of R and R₁ is H and the other is methyl.

38. (new): The cross-linker of claim 35 or 36, wherein n is 1, R₁ is methyl and R, R₂ and R₃ are H.

39. (new): The cross-linker of claim 35 or 36, wherein n is 1 and R, R₁, R₂, and R₃ are H.

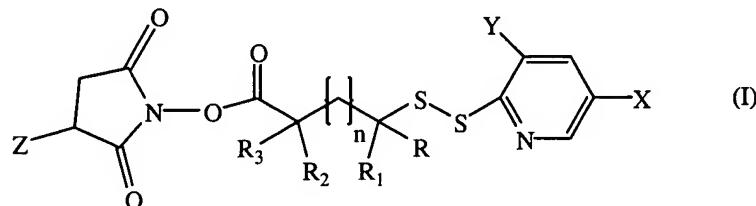
40. (new): The cross-linker of claim 35 or 36, wherein n is 1, R and R₁ are both methyl, and R₂ and R₃ are both H.

41. (new): A method of making a compound of formula (III):



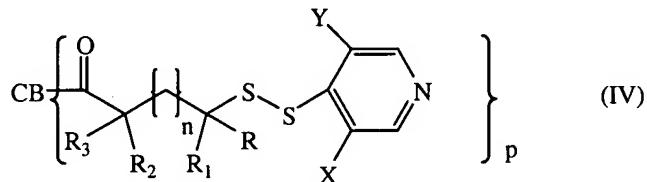
wherein CB represents a cell binding agent, R, R₁, R₂ and R₃ are the same or different and are H, methyl, ethyl, or linear, branched or cyclic alkyl having 3 to 6 carbon atoms, n is 0 or an integer from 1 to 4, X and Y are the same or different and are H, CONR₄R₅ or NO₂, provided that X and Y are not both H at the same time, R₄ and R₅ are the same or different and are each H, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, iso-butyl or tert-butyl, and p represents an integer of 1 to 10 or more,

comprising reacting the cell binding agent, CB, with a cross-linker of the formula (I):



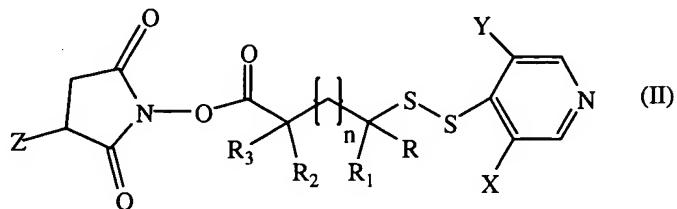
wherein Z is SO₃⁻M⁺ or H, wherein M⁺ represents a metal ion or a tetra alkyl ammonium ion.

42. (new): A method of making a compound of formula (IV):



wherein CB represents a cell binding agent, R, R₁, R₂ and R₃ are the same or different and are H, methyl, ethyl, or linear, branched or cyclic alkyl having 3 to 6 carbon atoms, n is 0 or an integer from 1 to 4, X and Y are the same or different and are H, CONR₄R₅ or NO₂, provided that X and Y are not both H at the same time, R₄ and R₅ are the same or different and are each H, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, iso-butyl or tert-butyl, and p represents an integer

of 1 to 10 or more,, comprising reacting the cell binding agent with a cross-linker of the formula (II):



wherein Z is SO_3^-M^+ or H, wherein M^+ represents a metal ion or a tetra alkyl ammonium ion.

43. (new): The method of claim 41 or 42, wherein the cell-binding agent is an antibody or an antigen binding fragment thereof.

44. (new): The method of claim 41 or 42, wherein the cell-binding agent is a monocloanal antibody or an antigen binding fragment thereof.

45. (new): the method of claim 41 or 42, wherein both of R and R_1 are H or methyl, or one of R and R_1 is H and the other is methyl.

46. (new): The method of claim 41 or 42, wherein n is 1, R_1 is methyl, and R, R_2 and R_3 are H.

47. (new): The method of claim 41 or 42, wherein n is 1 and R, R_1 , R_2 , and R_3 are H.

48. (new): The method of claim 41 or 42, wherein n is 1, R and R_1 are both methyl, and R_2 and R_3 are both H.